REMARKS

The claims remaining in this application are claims 29-32 and 34-38.

New claim 37 is supported at page 7, lines 15-17 of the specification, and new claim 38 is supported at page 11, line 32, to page 12, line 20, of the specification.

Claims 29-23 and 34-36 have been rejected under 35 USC § 112 as being insufficiently enabled by the original specification. This rejection is respectfully traversed.

It has long been established that in either a product or process claim an applicant may be permitted to define materials by the function which they perform. *In re Metcalfe*, 401 F.2d 1378, 161 USPQ 789 (Fed. Cir. 1969). Nothing in the cases cited by the examiner has overruled that principle.

The examiner has questions applicants' assertions that spreading depression is a well-recognized model for migraine.

There is attached to this response the article of Read et al., *Migraine & Headache Pathophysiology*, "Cortical Spreading depression and migraine," pp. 81-92, 1999. This review is a critical appraisal of current knowledge of the integrating role of cortical spreading depression in migraine. The authors conclude that changes in metabolic vascular and gene expression observed in experimental cortical spreading depression are complex and have a number of correlates in the clinic in migraine with and without aura (at page 89 under "conclusions").

Though said article focuses on cortical spreading depression and does not refer to retinal spreading depression, the theory of retinal spreading depression (RSD) is simply an extension of the cortical spreading depression (CSD) theory. Retinal spreading depression is analogous to cortical spreading depression. As stated in Dr.

Garcia-Ladona's declaration filed previously with the USPTO, spreading depression has been observed in all parts of the CNS, which includes the retina. In fact, the vertebrate retina belongs to the grey matter: see deLima et al., *Brain Research*, 614, p. 45-51, 1993, cited in the present application and referred to in said declaration, a copy of which is also attached hereto.

The examiner seems to base the rejection at least party on the assumption that the claimed method can be carried out only with either a 5-HT5 receptor agonist or a 5-HT5 receptor antagonist. This assumption, however, is not valid.

It is true that in principle one distinguishes between antagonist and agonistic effects that a drug may have on a particular receptor. However, this is only a rough classification. According to a more sophisticated (and realistic) view one has to differentiate between pure agonists, partial agonists, pure antagonists and partial antagonists (cf. the present specification on page 6, lines 23-26). To put it another way, any receptor agonist (perhaps with the exception of a 100% pure agonist) has a more or less pronounced antagonistic effect on the receptor. This is why one and the same drug may even elicit opposite effects depending on the state of the subject treated. For instance, dihydroergotamin may cause a vasodilation in one patient and a vasoconstriction in another patient.

It should be emphasized in this connection that it is not required to know the effector function of the claimed 5-HT5 binding partners in order to carry out the invention. For instance, the declaration we have filed with our previous submission shows that all the skilled person has to do is carry out the *in vitro* screening process and test the thus identified compounds in an appropriate animal model.

The screening process is set forth in the present application and enables the

skilled person to read out those compounds which have the required binding affinity for a 5-HT5 receptor and selectivity over the 5-HT1D receptor. Appropriate animal tests are also set forth in the present application and enable the testing of the resulting compounds in terms of antimigraine activity. All that is required for this screening and testing is routine experimentation.

Contrary to the examiner's allegation, merely binding of a compound to a receptor can be used to predict the biological effect of the compound. In the present case, for instance, there is evidence that the binding affinity for 5-HT5 receptor of a compound correlates with the efficacy of said compound in the treatment of migraine. That is to say, if one compares, for instance, the recommended therapeutic dose for known antimigraine drugs with their binding affinity for 5-HT5 receptor, it can be seen that the therapeutic dose increases as the binding affinity decreases (R(+)-Lisurid: 0.075 mg/day; Dihydroergotamin: 3 mg/day; Methylsergid: 2-6 mg/day; Sumatriptan: 100 mg/day; the 5-HT5 binding affinities are given in example 2 of the specification). Please note that this comparison does not belong to the prior art but is based on the present invention.

In vitro and *in vivo* methods have been fully set out in the present specification as alluded to above, and it would not be difficult or require undue experimentation on the part of one skilled in the art to identify suitable compounds without the use of undue experimentation. This is set forth in the *Wands* decision cited by the examiner and in *In re Angstaadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (Fed. Cir. 1976). Also see MPEP §§ 2164.01 and 2164.06.

All of the claims in the application have been rejected under 35 USC § 112 as lacking description in the specification. This rejection is respectfully traversed.

The claims are described *en haec verbis* throughout the specification. With respect to the dependent claims, for example, see page 4, lines 20-27.

The claims in US 6,048,850, which was the subject of the *University of Rochester* case cited by the examiner, were drawn to a method for selectively inhibiting PGHS-2 activity by administering a compound that selectively inhibits activity of the PGHS-2 gene product. Thus, what is claimed is to use a compound having a certain effect in a method for achieving said effect. This is a circular statement.

In contrast, the claims in the present application are directed to a method for treating particular diseases, i.e., migrainous cerebrovascular diseases such as migraine. Thus, the subject matter of the present claims is not simply confined to selectively inhibiting 5-HT5 receptor activity by administering compounds that selectively inhibit activity of the 5-HT5 receptor. On the contrary, the present invention teaches for the first time that cerebrovascular disorders such as migraine can be effectively treated with binding partners for the 5-HT5 receptor. Thus, it is the relationship between 5-HT5 binding affinity and the treatment of certain diseases which represent the contribution the present invention makes over the prior art.

The '850 patent, however, does not make such a contribution. Actually, the gist of the '850 patent is the cloning of the PGHS-2 gene and the provision of a screening method for identifying a compound that inhibits prostaglandin synthesis catalyzed by mammalian prostaglandin H synthase-2 (PGHS-2).

Two prior decisions cited in *University of Rochester* reflect the fact that physical properties can give a precise definition and that the principle set forth in *Metcalfe* is still correct. They are *Eli Lilly & Co. v. Barr Labs, Inc.*, 251 F.3d 955, 58 USPQ2d 1865 (Fed. Cir. 2001) and *Enzo Biochem., Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 63 USPQ

1609 (Fed. Cir. 2002). Indeed, as held in *Enzo*, disclosure of a nucleic acid can support a claim to nucleic acids that hybridize to it (i.e., that have a certain binding affinity for it).

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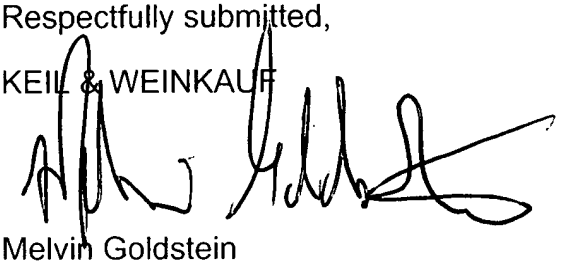
Respectfully submitted,

KEIL & WEINKAUF



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